UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MU

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/084,542	05/26/98	VITE G	LD125B

HM22/0816

BURTON RODNEY
BRISTOL-MYERS SQUIBB COMPANY
P O BOX 4000
PRINCETON NJ 08543-4000

EXAMINER	
COLEMAN, B	
ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/084,542	VITE et al.
Examiner	**Group Art Unit**
Brenda Coleman	1624

☒ Responsive to communication(s) filed on *Jun 30, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-6 are pending in the application.

This action is in response to applicants' amendment dated June 30, 2000. Claims 1 and 3-5 have been amended.

Response to Arguments

Applicant's arguments filed February 22, 2000 have been fully considered with the following effect:

1. The applicant's amendments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejections of the last office action which are hereby **withdrawn**.

In view of the amendment dated June 30, 2000, the following new grounds of rejection apply:

Information Disclosure Statement

2. The information disclosure statement filed January 20, 2000 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Those references which have been crossed through have not been considered at this time, because no copy is available. The applicants' are required to provide a legible copy of

each publication for consideration. The foreign patent documents have been obtained, but it is requested that the applicants' provide a copy of the journal articles to complete the record.

Improper Markush

3. Claims 1-6 are rejected as being an improper Markush grouping. The recited compounds, while possessing a common utility, present a variable core and, thus, the Markush groups represented by the terms W, Z_1 and Z_2, where W, Z_1 and Z_2 have variably different definitions, render the claims clearly improper.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While being enabling for treating carcinoma of the bladder, breast, colon, kidney, liver, etc., does not reasonably provide enablement for treatment of all tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to

a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1 and 4-6 are vague and indefinite in that the definition of Y contains a substituent which is not valence satisfied, i.e. H, NOR_{19}. If one of the bonds of the Y variable is to H and the other is to NOR_{19}, it is not known what else is bonded to the N atom.

b) Claims 1 and 4-6 are vague and indefinite in that the proviso at the end of the claim contains a reference to a variable R7, however, there is no variable R7 in the claim. It is believed that the applicants' intended R_7 (subscript).

c) Claim 3 is vague and indefinite in that the list of species includes a compound which is excluded by proviso in claim 1, i.e. the compound in lines 20-22 on page 67.

d) Claim 6 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by providing an antiangiogenic effect. It is unclear which diseases are mediated by antiangiogenic effect? Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different

pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug,

particularly in cancers, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless.--

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Balog et al., Tetrahedron Letters. Balog teaches the compounds of formula I where W and X are both O; R_1, R_2, R_6 and R_7 are H; R_3 and R_4 are methyl; R_8 is H or methyl; and Z_1 and Z_2 are CH_2. See examples 3 and 16 on page 4531.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hofle et al., WO 97/19086. The generic structure of Hofle encompasses the instantly claimed compounds (see Formula 1, page 1) and for the same uses as claimed herein. The examples differ only in the nature of the R substituent. Page 4, line 2 defines the substituent R as H or C_{1-4} alkyl. Compounds of the instant invention are generically embraced by Hofle in view of the interchange ability of the R substituent of the epothilone ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example ethyl which is the next adjacent homolog of the methyl group which is part of the proviso at the end of claim 1

as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Monday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
August 14, 2000